Preclinical development and qualification of ZFN-mediated CCR5 disruption in human hematopoietic stem/progenitor cells.

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Public Summary:
Gene therapy for HIV-1 infection is a promising alternative to lifelong combination antiviral drug treatment. Chemokine receptor 5 (CCR5) is the co-receptor required for R5-tropic HIV-1 infection of human cells. Deletion of CCR5 renders cells resistant to R5-tropic HIV-1 infection, and the potential for cure has been shown through allogeneic stem cell transplantation with naturally occurring homozygous deletion of CCR5 in donor hematopoietic stem/progenitor cells (HSPC). The requirement for HLA-matched HSPC bearing homozygous CCR5 deletions prohibits widespread application of this approach. Thus, a strategy to disrupt CCR5 genomic sequences in HSPC using zinc finger nucleases was developed. Following discussions with regulatory agencies, we conducted IND-enabling preclinical in vitro and in vivo testing to demonstrate the feasibility and (preclinical) safety of zinc finger nucleases-based CCR5 disruption in HSPC. We report here the clinical-scale manufacturing process necessary to deliver CCR5-specific zinc finger nucleases mRNA to HSPC using electroporation and the preclinical safety data. Our results demonstrate effective biallelic CCR5 disruption in up to 72.9% of modified colony forming units from adult mobilized HSPC with maintenance of hematopoietic potential in vitro and in vivo.

Scientific Abstract:
Gene therapy for HIV-1 infection is a promising alternative to lifelong combination antiviral drug treatment. Chemokine receptor 5 (CCR5) is the coreceptor required for R5-tropic HIV-1 infection of human cells. Deletion of CCR5 renders cells resistant to R5-tropic HIV-1 infection, and the potential for cure has been shown through allogeneic stem cell transplantation with naturally occurring homozygous deletion of CCR5 in donor hematopoietic stem/progenitor cells (HSPC). The requirement for HLA-matched HSPC bearing homozygous CCR5 deletions prohibits widespread application of this approach. Thus, a strategy to disrupt CCR5 genomic sequences in HSPC using zinc finger nucleases was developed. Following discussions with regulatory agencies, we conducted IND-enabling preclinical in vitro and in vivo testing to demonstrate the feasibility and (preclinical) safety of zinc finger nucleases-based CCR5 disruption in HSPC. We report here the clinical-scale manufacturing process necessary to deliver CCR5-specific zinc finger nucleases mRNA to HSPC using electroporation and the preclinical safety data. Our results demonstrate effective biallelic CCR5 disruption in up to 72.9% of modified colony forming units from adult mobilized HSPC with maintenance of hematopoietic potential in vitro and in vivo. Tumorigenicity studies demonstrated initial product safety; further safety and feasibility studies are ongoing in subjects infected with HIV-1 (NCT02500849@clinicaltrials.gov).